REMARKS

Applicant has canceled claim 2 and amended claims 1, 3, 5, 7, 16, and 17 to recite factor VII or factor VIIa polypeptide. The dependency of claims 3, 5, 7, and 16 has been amended. No new matter has been added. Applicant respectfully requests reconsideration and allowance of claims 1, 3-14, and 16-17 in view of the above amendments and following remarks.

Applicant notes that references AG and AH on the Form 1449 submitted with the Information Disclosure Statement of September 21, 1999, was not initialed. Applicant respectfully requests that an initialed copy of the Form 1449 be returned to Applicant, indicating that references AG and AH have been considered.

Objections

The Examiner objected to claims 1-14, 16 and 17 because they contain non-elected subject matter. Applicant has canceled the non-elected subject matter in claims 1-14 and 16-17 without prejudice to further prosecution.

Sequence Listing

The Examiner asserted that the Applicants are not in compliance with the sequence listing requirements. The Examiner suggested "following the procedure adopted in the parent specification."

Applicant submits that the requirements for applications containing nucleotide or amino acid sequences have been met. As indicated previously, sequence identifiers are present throughout the specification and are not necessary in the drawings or in the claims. In particular, the specification contains a sequence identifier for the wild-type Factor VII at page 12, lines 15-16. The specification also describes how the amino acid positions of the polypeptides are numbered. See, the specification at page 9, lines 14-19, which indicates that amino acid positions are numbered according to Factor IX, and that Factor VII has one less amino acid (position 4) and must be adjusted accordingly. Thus, when a claim recites a particular position such as amino acid 11 for Factor VII, it is actually position 10 of Factor VII in the sequence

listing. As the claims recite particular positions within Factor VII that contain substitutions, the sequence identifiers in the application can be used for searches.

The Examiner also asked for the SEQ ID NO. of Factor VII(a), and wondered how the sequence of factors VII and VIIa differed.

Factor VII is a zymogen, or inactive precursor, that is proteolytically cleaved to form Factor VIIa. The peptide bond between arginine 152 and isoleucine 153 is cleaved in factor VII to form factor VIIa. See, specification at page 2, line 1 and U.S. Patent No. 5,788,965 (reference AA on the supplemental information disclosure statement of August 17, 2000). Thus, the sequence of Factor VIIa is provided by the sequence of Factor VII.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-14, 16 and 17 under 35 U.S.C. § 112, first paragraph, for lack of written description. The Examiner asserted that "Applicant did not have the possession of Factor VII "comprising" as the expression encompasses the entire polypeptide sequence in addition to the intended segment as set forth in the specification as "a modified GLA domain" at the time the invention was made. Moreover, the nature of the amino acid being substituted does not encompass the various known amino acids having diverse properties (also not shown in the specification)." Claims 1-14, 16 and 17 also were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner asserted that "Factor VII or VIIa is a protein having a vast number of amino acids in its sequence and one of skill in the art would expect that the preparation and use of the modified protein would call for undue experimentation. Further, the specification is not enabled for substitution of all kinds of amino acids, regardless of their structure and/or properties in the designated position in the GLA domain." Applicant respectfully traverses.

Claims 1-14, and 16 relate to a factor VII polypeptide that has a modified GLA domain that includes at least one amino acid substitution at amino acid residue 11 or 29 and that has enhanced membrane binding affinity relative to a corresponding native Factor VII polypeptide. Claim 17 relates to a factor VII polypeptide that includes an aspartic acid residue at amino acid 33.

The nucleotide and amino acid sequences of the entire bovine and human factor VII polypeptides were known at the time of filing. The specification provides the GenBank Accession number as well as a reference for the wild type factor VII cDNA. See, the specification at page 23, lines 4-6. Furthermore, the wild-type amino acid sequences for the human and bovine factor VII polypeptides GLA domain (SEQ ID NOS: 3 and 4, respectively) are provided at page 12, lines 15-16 of the specification.

The specification also describes how to make polypeptides of the invention, including full-length polypeptides. For example, Example 1 describes the production of full-length factor VII with enhanced membrane binding affinity using a polymerase chain reaction (PCR) strategy. PCR primers are denoted by nucleotide location. See, for example, page 23, lines 13-16. Nucleic acid fragments were generated with this strategy, and ligated to produce a nucleic acid encoding a full-length polypeptide. It would be apparent to a person of ordinary skill in the art that polypeptide fragments could be produced from these or other nucleic acid fragments in the same manner. Detailed methods also are provided for the purification of factor VII. See, for example, page 24, lines 3-9 and Example 2, page 30, line 21 through page 31, line 26.

Furthermore, the specification describes techniques for determining membrane affinity of factor VII polypeptides. In general, vesicles of phosphatidylserine and phospatidylcholine were prepared, and protein was added at different weight ratios. Protein-membrane binding then was assayed by a light scattering technique. See, specification, page 24, line 20 through page 25, line 20. Thus, Applicant was in possession of Factor VII comprising the GLA domain of factor VII as well as the full-length polypeptide, and enabled one of ordinary skill in the art to make and use such polypeptides.

With respect to the Examiner's comments regarding substitution of amino acid residues, Applicant submits that the specification provides a number of examples of amino acid residues that can be substituted at positions 11 and 29. The specification indicates that conservative amino acid substitutions that replace an amino acid with an amino acid residue of the same class can be made in the GLA domain. See, specification at page 9, lines 23-24. Non-conservative substitutions, which include replacing an amino acid with an amino acid of a different class, also can be made in the GLA domain. See, specification at page 9, lines 24-25. The specification provides examples of non-conservative amino acid substitutions, including substitutions of basic

amino acids for non-polar amino acids, or polar amino acids for acidic amino acids. See specification at page 10, lines 3-5. In addition, the specification indicates that a glutamic acid, a glutamine, an asparagine, or an aspartic acid residue can be substituted at amino acid 11, and a phenylalanine or glutamic acid residue can be substituted at amino acid 29 of factor VII. See, specification at page 12, lines 17-21. Furthermore, claim 17 recites that it is an aspartic acid residue that is substituted at amino acid 33. As described above, the specification describes how to produce polypeptides having such substitutions at these positions and provides a test to determine if particular amino acid substitutions enhance membrane binding of the polypeptide. Thus, Applicant was in possession of factor VII having at least one substitution at position 11 or 29, or having an aspartic acid residue at amino acid 33, and enabled one of ordinary skill in the art to produce such polypeptides.

In view of the above remarks, the Examiner is requested to withdraw the rejection of claims 1-14, 16, and 17 under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-14, 16 and 17 under 35 U.S.C. § 112, second paragraph. The Examiner asserted that the "claims are indefinite and unclear regarding the location and the number of amino acids in the 'GLA domain'." Applicant respectfully traverses.

The specification clearly indicates at page 9, lines 10-12, that the GLA domain contains 9-13 γ-carboxyglutamic acid residues in the N-terminal region of the polypeptide, typically from amino acid 1 to about amino acid 45. Thus, one of ordinary skill in the art would understand the term "GLA domain."

The Examiner also asserted that the "claims are indefinite and unclear as to the nature and/or properties of the amino acids being substituted for the native amino acids." Applicant respectfully traverses.

As discussed above, the specification provides a number of examples of amino acid residues that can be substituted at positions 11 and 29. The specification indicates conservative or non-conservative substitutions can be made. In addition, the specification indicates that a glutamic acid, a glutamine, an asparagine, or an aspartic acid residue can be substituted at amino acid 11, or a phenylalanine or glutamic acid residue can be substituted at amino acid 29. Claim

17 recites that it is an aspartic acid residue that is substituted at amino acid 33. The specification also provides guidance on how to make such modified factor VII polypeptides and measure membrane affinity of modified factor VII polypeptides. Thus, Applicant submits that claims 1-14, 16 and 17 are sufficiently definite under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1-14, 16 and 17 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,516,640 (the '640 patent). The Examiner characterized the '640 patent as showing "the amino acid sequences of GLA regions of h-FVII is known in the art", and cited the TABLE at column 3. The Examiner contended that to "make a conservative substitution at any position in the peptide is expected to result in a peptide having about the same properties as the unsubstituted peptide. One of ordinary skill in the art would be motivated to conservatively substitute (or delete) an amino acid in the chain depending, on the method of preparation, ease of obtaining the starting materials and etc." Table 2 of U.S Patent No. 5,093,317 was cited to show the conservative amino acid replacements. Applicant respectfully traverses.

The '640 patent provides an immunoassay for detecting vitamin K-dependent proteins that are incompletely carboxylated (PIVKAs). The amino acid sequences of the GLA domain of human factor VII and other PIVKAs are provided in the '640 patent. The '317 patent provides modified neuroactive polypeptides such as insulin-like growth factor I and II. A table is provided in the '317 patent that lists conservative amino acid replacements for 18 amino acids.

The combination of the '640 and '317 patents does not teach or suggest the presently claimed factor VII polypeptides. In particular, the combination of cited art does not teach or suggest that factor VII polypeptides containing substitutions of amino acid residues at positions 11 or 29 would have enhanced membrane binding affinity. Furthermore, the combination of cited art does not teach or suggest a factor VII polypeptide that includes an aspartic acid residue at amino acid 33.

The Examiner contends that making "a conservative substitution at any position in the peptide is expected to result in a peptide having about the same properties as the unsubstituted peptide". Applicant submits that independent claim 1 recites that the modified GLA domain

results in a polypeptide having enhanced membrane binding affinity. Thus, the claimed polypeptides do not have the same binding properties as the native polypeptide. In view of the above remarks, the Examiner is requested to withdraw the rejection of claims 1-14, 16, and 17 under 35 U.S.C. § 103.

CONCLUSION

Applicant submits that all claims are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if it is felt that such would advance prosecution of the application.

Attached is a marked-up version of the changes being made by the current amendment.

No fees are due as this response is being filed before expiration of the shortened statutory period. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 6/18/01

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Version with markings to show changes made

In the specification:

Paragraph beginning at page 1, line 5, has been amended as follows:

This application is a continuation-in-part of U.S. Serial No. 08/955,636, filed [on] October 23, 1997, now U.S. Patent No. 6,017,882.

In the claims:

Claim 2 has been canceled.
Claim 1,3, 5, 7, 16, and 17 have been amended as follows:

1. (Amended) A Factor VII or Factor [IX] VIIa polypeptide comprising a modified GLA domain that enhances membrane binding affinity of said polypeptide relative to a corresponding native Factor VII or Factor [IX] VIIa polypeptide, said modified GLA domain comprising at least one amino acid substitution at residue 11 or 29.

3. (Amended) The polypeptide of claim [2] 1, wherein a glutamine, a glutamic acid, an aspartic acid, or an asparagine residue is substituted at residue 11.

5. (Amended) The polypeptide of claim [2] 1, wherein a glutamic acid or a phenylalanine residue is substituted at residue 29.

7. (Amended) The polypeptide of claim [2] 1, wherein said modified domain further comprises an amino acid substitution at residue 33.

16. (Amended) The polypeptide of claim [2] 1, wherein said polypeptide comprises active-site modified Factor VIIa.

17. (Amended) A Factor VII or Factor [IX] VIIa polypeptide comprising a modified GLA domain that enhances membrane binding affinity of said polypeptide relative to a corresponding native Factor VII or Factor [IX] VIIa polypeptide, said modified GLA domain comprising an aspartic acid residue at amino acid 33.

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